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PYRIDYLPHENYL NITROGEN HETEROCYCLE-SUBSTITUTED CARBINOLS AND DERIVATIVES THEREOF WITH ANTI-INFLAMMATORY ACTIVITY

Abstract:

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(54) Title: PYRIDYLPHENYL NITROGEN HETEROCYCLE-SUBSTITUTED CARBINOLS AND DERIVATIVES THEREOF WITH ANTI-INFLAMMATORY ACTIVITY

(57) Abstract

Pyridylphenyl nitrogen heterocycle-substituted carbinols and derivatives thereof and pharmaceutical compositions containing such compounds are useful for treating inflammatory diseases in mammals.

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TITLE

PYRIDYLPHENYL NITROGEN HETEROCYCLE-SUBSTITUTED CARBINOLS AND DERIVATIVES THEREOF WITH ANTI-INFLAMMATORY ACTIVITY

BACKGROUND OF THE INVENTION

FIELD OF INVENTION

This invention relates to pyridylphenyl nitrogen heterocycle-substituted carbinols, pharmaceutical compositions containing them, methods of using them to treat inflammatory disease in mammals and processes for preparing said compounds.

BACKGROUND

Inflammatory diseases are a widespread cause of human suffering and loss of function. Additionally, the treatment of patients with these diseases represents a very large expense in terms of money, facilities and personnel. The incidence of many such diseases is expected to rise in the future as life expectancy and the median age of the population continue to increase.

Inflammatory diseases are known which affect many diverse tissues and organs in the body. Examples of diseases in which the inflammation is most apparent in the joints and related connective tissue are diseases such as osteoarthritis, rheumatoid arthritis, tendonitis and bursitis. These diseases are most often treated with nonsteroidal anti-inflammatory agents such as aspirin, ibuprofen, and piroxicam, or with anti-inflammatory glucocorticosteroids. However, these treatments are deficient either due to a lack of efficacy in completely controlling the disease process, or due to unacceptable toxic side effects. Rheumatoid arthritis in particular is a representative of a class of systemic diseases thought to possess an auto-immunity component, which are treated additionally with anti-proliferative agents and with so-called disease-

modifying agents such as gold salts, penicillamine and antimalarial agents. These drugs also possess severe toxic effects which limit their utility.

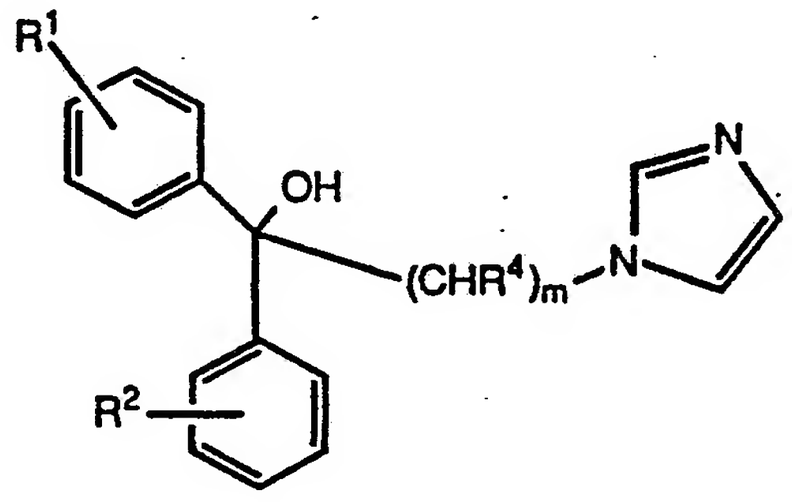
Examples of diseases in which the inflammation is most apparent in the skin are psoriasis, contact dermatitis, atopic dermatitis, and eczema. These diseases are usually treated with anti-inflammatory glucocorticosteroids, or (in the case of psoriasis) with psoralen in combination with UV-A light (PUVA), or with coal tar preparations or antiproliferative agents. Again, these treatments are often unacceptable to patients and also have a poor degree of efficacy and/or unacceptable side effects.

Inflammatory diseases of other tissues and organs are also of concern, for example inflammatory bowel disease and ocular inflammation such as uveitis and conjunctivitis. Treatments for these diseases, primarily using glucocorticosteroids, also lack efficacy and freedom from toxic effects.

Thus, there is a continuing medical need for safe, efficacious anti-inflammatory agents for use as systemic and/or topical therapy for inflammatory diseases.

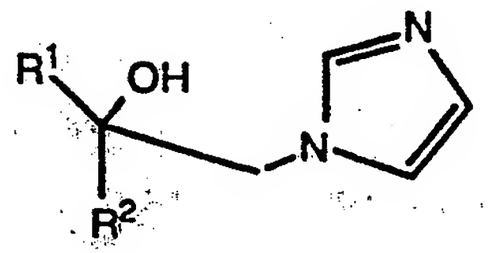
PRIOR ART

Commonly assigned U.S. Patent 4,859,693 discloses the anti-inflammatory activity of carbinoloimidazoles with the structure



wherein R^1 and R^2 are H, F, Cl, Br, CH_3, CF_3, or $S(O)_nR^3$ (n = 0, 1, or 2); R^3 is C_1-C_4 alkyl; m is 1 to 3; and R^4 is H or C_1-C_4 alkyl, provided that when R^4 is alkyl then m is 1.

German Patent 2920375 and U.S. Patent 4,301,166 disclose, inter alia, fungicidal compounds with the structure

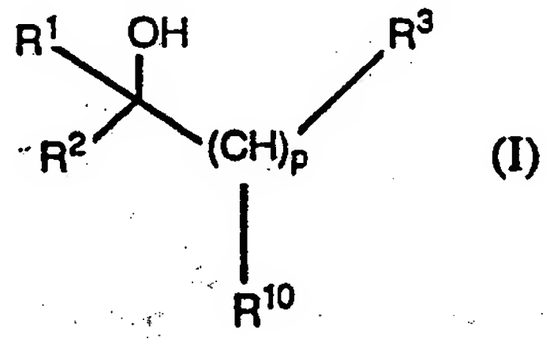


wherein R^1 is optionally substituted phenyl and R^2 is optionally substituted biphenyl. German Patent 2920374 discloses compounds of the same structure except that the imidazole group is replaced with triazole. These triazoles also have fungicidal activity.

None of the above-described references disclose the compounds of the present invention or suggest that such compounds would possess activity as anti-inflammatory agents.

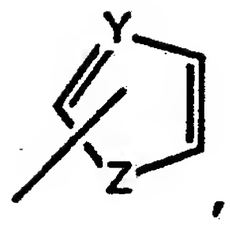
SUMMARY OF THE INVENTION

According to the present invention provided are compounds having the formula:



(I)

in the form of an individual stereoisomer, a non-racemic stereoisomer mixture or a racemic mixture or a pharmaceutically acceptable salt thereof wherein:

R^1 is 2-, 3-, or 4-pyridyl,  , R^7, or phenyl optionally substituted with 1-3 substituents independently selected from the group consisting of F, Cl, Br, C_1-C_4 alkyl, C_1-C_4 perfluroalkyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, CHO, $COOR^4$, C_1-C_4 acyl, NR^5R^6, C_1-C_4 alkoxy or CH_2OR^8;

R^2 and R^7 independently are phenyl substituted in the ortho, meta, or para position with R^9;

R^3 is imidazole, 1,2,4-triazole, 1,3,4-triazole, benzimidazole, pyrrole, indole, or pyrazole provided that R^3 is bonded to the remainder of the structure through a nitrogen atom;

R^4, R^8, and R^{10} independently are H or C_1-C_4 alkyl;

R^5 and R^6 independently are H, C_1-C_4 alkyl, or taken together are $(CH_2)m$ wherein m is 4-5;

R^9 is 2-, 3-, or 4-pyridyl;

Y is N or CH;

Z is S, O, or NR^{11};

R^{11} is H or C_1-C_4 alkyl; and

p is 1-4 provided that when p is greater than 1, then R^{10} is H.

Also provided are pharmaceutical compositions comprising compounds of Formula I as individual stereoisomers, non-racemic stereoisomer mixtures,

racemic mixtures or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier.

Further provided are methods of using compounds of Formula I to treat an inflammatory disease in a mammal.

Additionally provided are processes for preparing the compounds of Formula I as described hereinafter.

PREFERRED EMBODIMENTS

Preferred compounds are those compounds of Formula I as described above wherein:

(a) p is 1; and/or

(b) R^3 is imidazole or triazole.

More preferred compounds are those preferred compounds wherein:

(a) R^3 is imidazole; and/or

(b) R^{10} is H; and/or

(c) R^1 is phenyl optionally substituted by one or two of the substituents listed above.

Most preferred compounds are those more preferred compounds wherein:

(a) R^1 is mono- or di-substituted phenyl with one of the substituents at the 4-position; and/or

(b) R^2 is 4-(4-pyridylphenyl) or 3-(4-pyridylphenyl).

Specifically preferred compounds are :

a) 1-(4-fluorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

b) 1-(2,4-difluorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

c) 1-(4-fluorophenyl)-1-[3-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

d) 1-(4-methylphenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

e) 1-(4-methoxyphenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

f) 1-(4-trifluoromethylphenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

g) 1-(4-chlorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

DETAILED DESCRIPTION OF THE INVENTION

SYNTHESIS

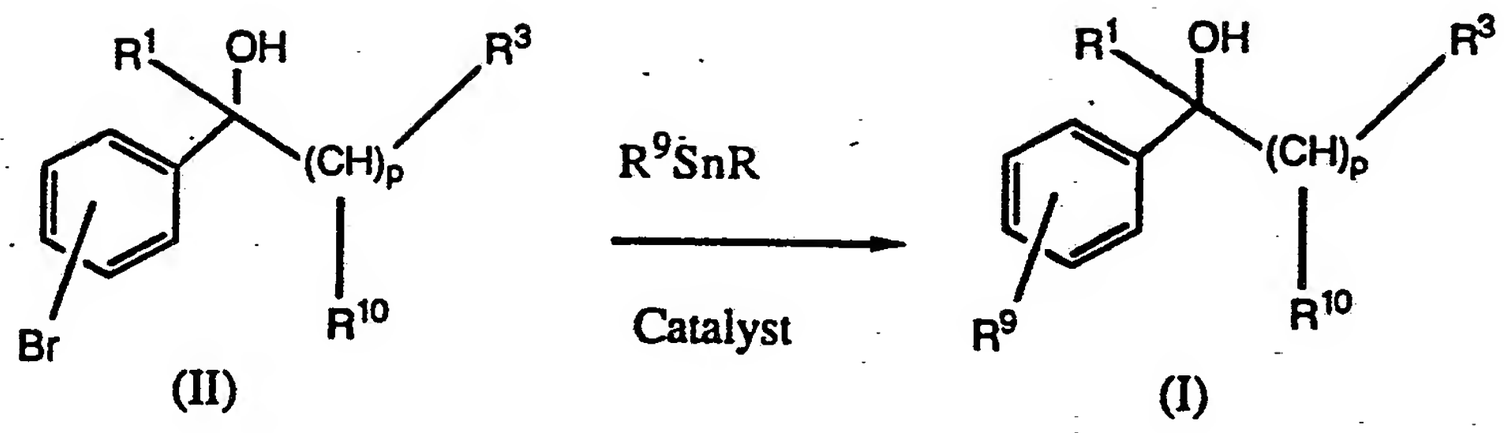
The compounds of Formula (I) can be prepared using the reactions and techniques described below. The reactions are usually performed in a solvent appropriate to the reagents and materials employed, and suitable for the transformation being effected. In some cases functional groups on the starting materials may need to be protected by standard protecting groups reported in the chemical literature which are well known to one skilled in the art. In some cases, substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternative methods described herein must then be used.

Many of the compounds of Formula (I) possess one or more chiral carbon atoms, allowing the occurrence of different enantiomers and/or diastereomers. In those cases where enantiomers are possible, the separate enantiomers may be obtained in pure or enantiomerically enriched form either by starting from a single enantiomer of a starting material (in those cases where the starting material also possesses the chiral carbon atom), or by resolution of the racemic mixture using standard methods. Diastereomers may generally also be separated using standard methods such as chromatography or fractional crystallization.

The compounds of Formula (I) may be converted to acid addition salts by treatment with a suitable pharmaceutically acceptable acid, using standard methods.

Several methods may be used to prepare the compounds of Formula (I). In Method A (Scheme 1), a bromophenyl compound (II) may be reacted with a pyridylstannane (R^9SnR, where R = C_1-C_4 alkyl) such as a pyridyltrimethylstannane in the presence of an appropriate transition metal catalyst to provide the desired compound of Formula (I). Examples of suitable catalysts are complexes of palladium and nickel, such as bis(triphenylphosphine) palladium(II) chloride. The reactions are usually conducted in a suitable organic solvent or solvent mixture such as tetrahydrofuran, N,N-dimethylformamide, or mixtures of N,N-dimethylformamide and an amine such as triethylamine. The reactions are usually conducted at temperatures above room temperature but below the boiling point of the solvent, preferably between about 50 and 100°C. An example of such a transition-metal mediated coupling between a pyridylstannane and a substituted bromobenzene from the chemical literature is given by Bailey, Tetrahedron Lett. 1986, 27, 4407. The starting materials for this method are known in the chemical literature, or may be prepared using known methods. Bromophenyl compounds of formula (II) may be prepared, for example, using methods disclosed by commonly assigned U.S. Patent 4,859,693. Trimethylstannylpyridines have also been reported in the chemical literature, for example by Yamamoto and Yanagi, Heterocycles 1981, 16, 1161. Method A is exemplified by the procedure of Example 1.

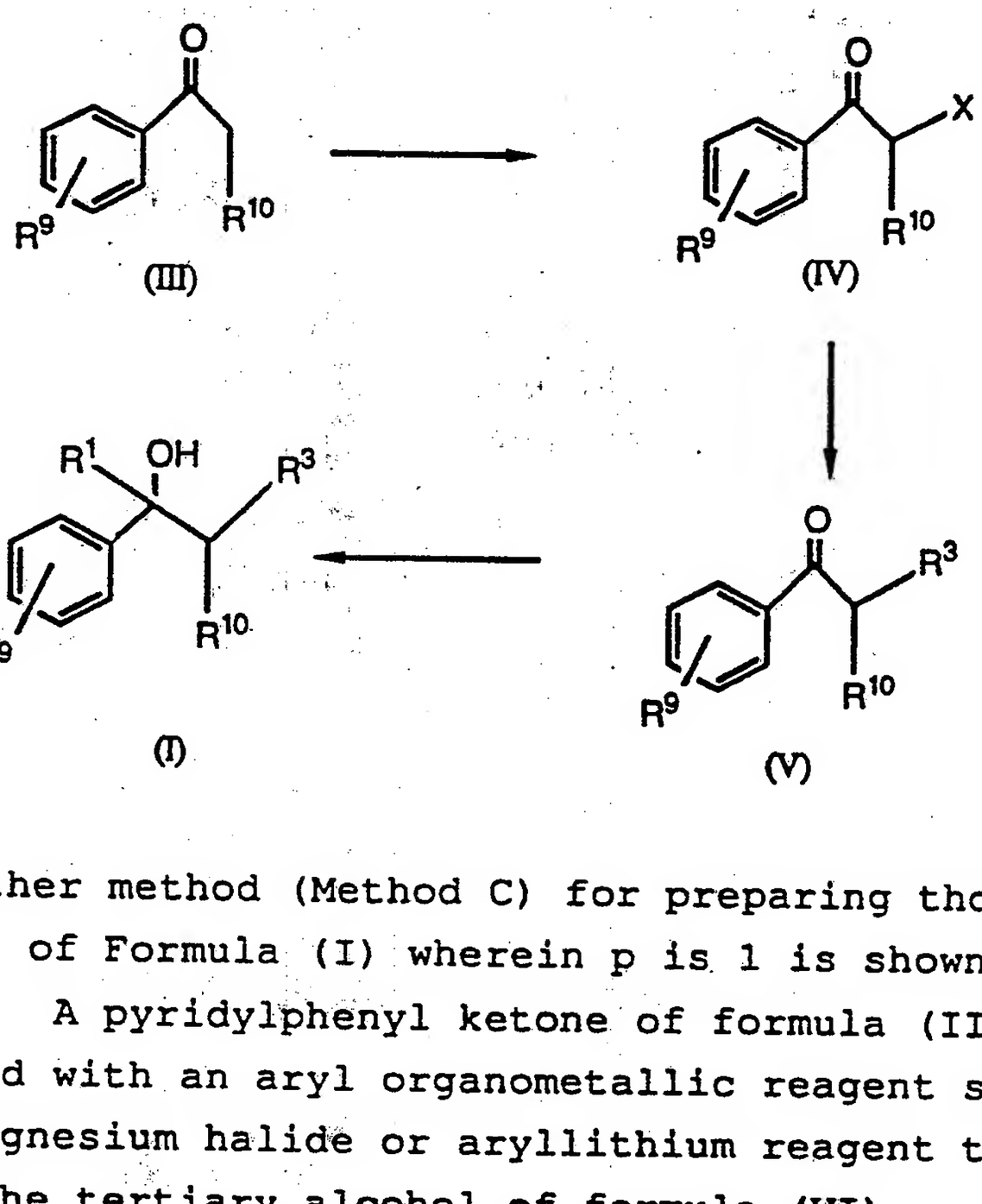
SCHEME 1



A second method (Method B) for preparing those compounds of Formula (I) wherein p is 1 is shown in Scheme 2. A pyridylphenyl ketone of formula (III) may be converted to the alpha-halo derivative (IV) where X is bromine or chlorine. These transformations are well known in the chemical literature, and may be performed using reagents such as bromine or chlorine in the presence of an acidic catalyst such as hydrobromic acid. A useful solvent for these reactions is acetic acid. The halo-derivative (IV) may then be reacted with a nitrogen heterocycle R^3H or with a metal salt of a heterocycle R^3M where M is, for example, sodium or potassium to give the substituted compound (V). The nitrogen heterocycle may be converted to the metal salt and subsequently be reacted with the compound of formula (IV), or the nitrogen heterocycle may be combined with a suitable base such as potassium tert-butoxide directly in the reaction mixture to form the metal salt in situ. The desired compound of formula (I) may be prepared from the intermediate of formula (V) by treatment with an organometallic compound R^1M^1, where M^1 may be, for example, lithium, magnesium halide, or cerium halide. Organocerium halides are preferred for this reaction, since hydrogen abstraction from (V), which leads to recovered starting material, is often minimized by the use of these reagents. The general method of

preparation of 1,1-diaryl-2-azolylethanols and derivatives by organometallic addition to an aryl azolylmethyl ketone has been disclosed previously, for example, in U.S. Patent 4,301,166 and U.S. Patent 4,689,337. Method B is exemplified by the procedure of Example 21.

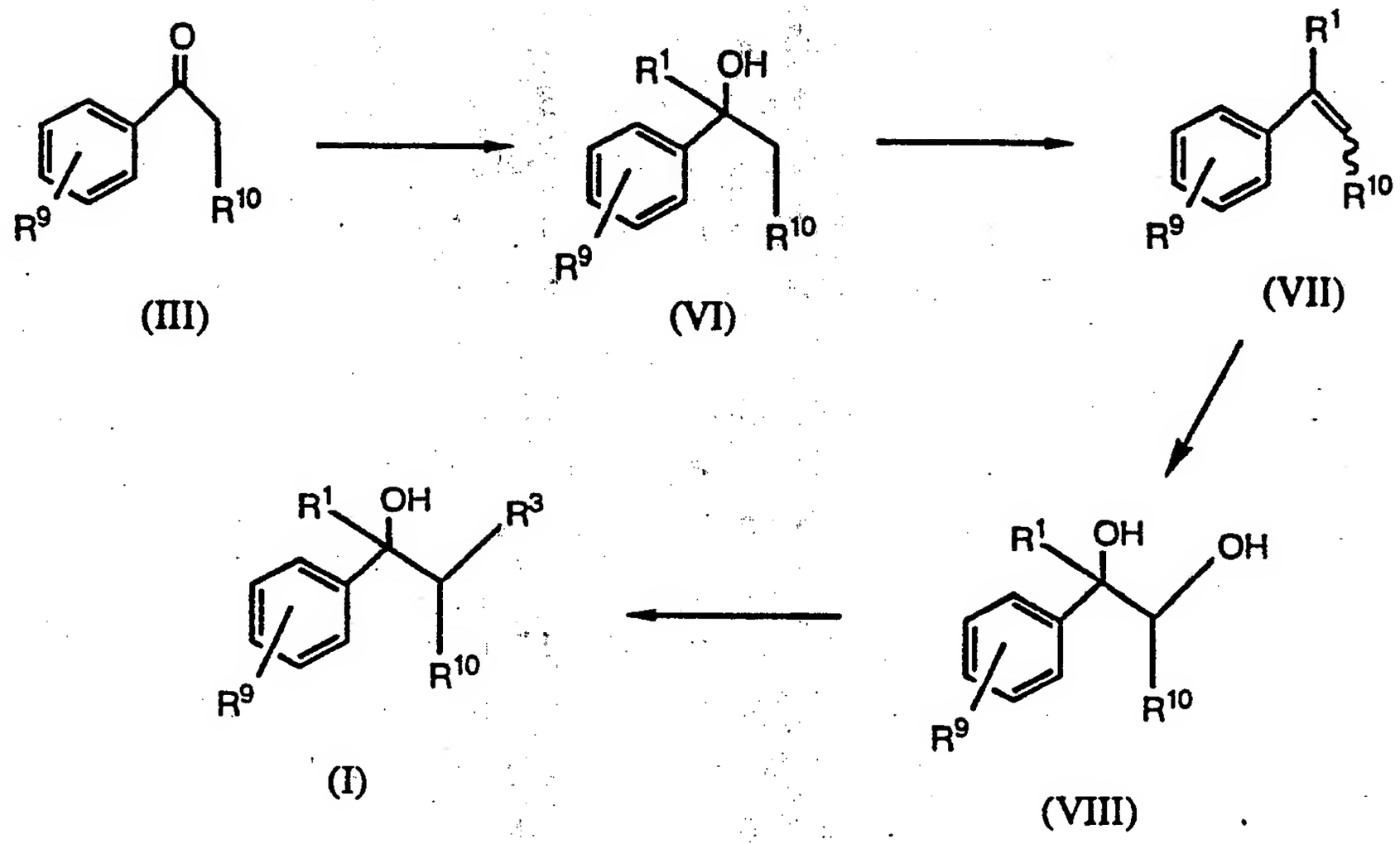
SCHEME 2



Another method (Method C) for preparing those compounds of Formula (I) wherein p is 1 is shown in Scheme 3. A pyridylphenyl ketone of formula (III) may be reacted with an aryl organometallic reagent such as an arylmagnesium halide or aryllithium reagent to provide the tertiary alcohol of formula (VI). Dehydration of this alcohol to the olefin of formula (VII) may be performed using standard chemical techniques, for example by treatment with an acid catalyst and azeotropic removal of the water formed in the reaction. The olefin may be converted to the vicinal diol of formula (VIII) using standard oxidation techniques, for example, by treatment with osmium

tetroxide, optionally in the presence of an auxiliary oxidant such as N-methylmorpholine N-oxide. The compound of formula (VIII) may be converted to the desired compound of formula (I) by conversion of the less sterically-hindered alcohol to a better leaving group, for example by conversion to a sulfonate ester such as the methanesulfonate ester, using well known methods. This intermediate may then be reacted with a nitrogen heterocycle R^3H, or with a metal salt of a nitrogen heterocycle R^3M where M is, for example, sodium or potassium. The nitrogen heterocycle may be converted to the metal salt and subsequently be reacted with the compound of formula (VIII), or the nitrogen heterocycle may be combined with a suitable base such as potassium tert-butoxide directly in the reaction mixture to form the metal salt in situ. (The general method for converting a diaryl alkanediol such as (VIII) to a diarylimidazolylethanol such as (I) is disclosed in U.S. Patent 4,859,693.) Method C is exemplified by the procedure of Example 41.

SCHEME 3

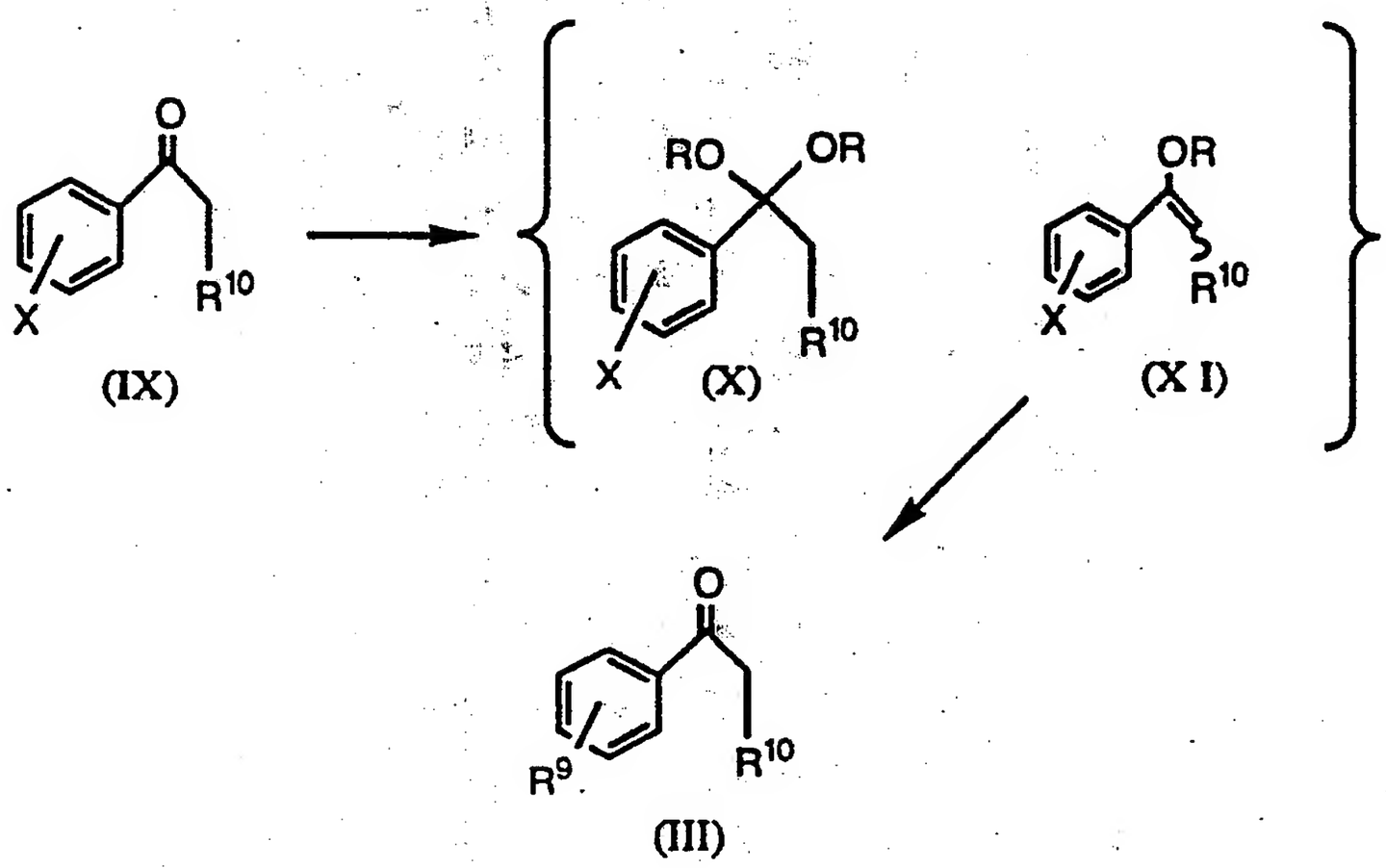


Certain substituents on R^1 in compounds of Formula (I) wherein R^1 is substituted phenyl may be prepared from other compounds of Formula (I) by standard chemical manipulations of substituents which are well known to one skilled in the art. The preparation of a compound of Formula (I) by functional group manipulation of another compound of Formula (I) is demonstrated by Examples 61 and 62.

The pyridylphenyl ketones which are starting materials for Methods B and C may be prepared from bromophenyl ketones or iodophenyl ketones of formula (IX), wherein X is Br or I, as shown in Scheme 4. The ketone of formula (IX) may be first converted to a protected form of the ketone by treatment with a primary alcohol in the presence of an aliphatic orthoester of this alcohol and an acid catalyst, using standard methods. Depending on the nature of the ketone (IX), either the ketal (X) or the enol ether (XI) may be obtained. Both of these are suitable for use in the

subsequent reaction. The protected ketone of formula (X) or (XI) may then be converted to an organometallic derivative such as the magnesium halide or lithium derivative using standard methods. This organometallic reagent may be used directly, or may preferably be further converted by transmetallation to a different organometallic derivative such as the organozinc reagent, which is more suitable for use in the subsequent coupling reaction. The organometallic reagent may then be treated with a halopyridine in the presence of a transition metal catalyst, such as a nickel or palladium catalyst, to provide after acid hydrolysis the corresponding compound of formula (III). (An example of forming an unsymmetrical biaryl using the nickel- or palladium-catalyzed coupling of an arylzinc reagent with an aryl halide has been reported by Negishi et al., J. Org. Chem. 1977, 42, 1821.)

SCHEME 4



Examples of the preparation of pyridylphenyl ketone starting materials are given below. All temperatures are in degrees Celsius. All reactions are performed under an atmosphere of dry nitrogen. Concentration under reduced pressure is performed with a rotary evaporator using a water aspirator. Nuclear magnetic resonance (NMR) spectra were obtained at a field strength of 200 or 300 MHz; abbreviations for NMR data are as follows: s = singlet, d = doublet, m = multiplet, $CDCl_3$ = deuterochloroform solvent. Peak positions for NMR data are reported as parts per million downfield from the internal standard tetramethylsilane. All parts and percentages are by weight unless otherwise indicated.

Preparation of Pyridylphenyl Ketone Starting Materials

a. Preparation of 3-(2-Acetylphenyl)pyridine A mixture of 2'-bromoacetophenone (75.0 g, 0.375 mol), trimethyl orthoformate (210 mL, 1.91 mol), methanol (210 mL), and Dowex® 50X2-400 acid ion exchange resin (7.5 g)

was heated at reflux for 1.5 h. The mixture was cooled, filtered through Celite®, and concentrated. Vacuum distillation of the residue gave 1-methoxy-2'-bromostyrene (71.66 g, 90%). NMR (CDCl3) 7.8-7.1 (4H), 4.40 (d, 1H), 4.30 (d, 1H), 3.75 (s, 3H). A solution of this material (1.84 g, 7.5 mmol) in tetrahydrofuran (10 mL) was cooled to -78° and treated over 4 min with tert-butyllithium (1.7 M in pentane; 8.8 mL, 15 mmol). After stirring for 30 min, the solution was warmed to 0° and added by cannula to a slurry of zinc chloride (freshly fused and powdered; 1.02 g, 7.5 mmol) in tetrahydrofuran (15 mL) at 0°. The mixture was stirred for 60 min at room temperature. In a separate flask, a suspension of bis(triphenylphosphine) palladium (II) chloride (0.165 g, 0.23 mmol) in tetrahydrofuran (7.5 mL) was treated with diisobutylaluminum hydride (1.0 M in toluene; 0.50 mL, 0.50 mmol). The organozinc solution was added to the palladium catalyst mixture by cannula, and the resulting mixture was treated with 3-bromopyridine (0.72 mL, 7.5 mmol). The mixture was stirred at room temperature overnight, and was concentrated. The residue was partitioned between ether and 6M aqueous sodium hydroxide. The ether layer was washed with water and brine, then was dried over magnesium sulfate and concentrated to give a yellow oil. This was stirred in 1 N hydrochloric acid (5 mL) and tetrahydrofuran (10 mL) at room temperature for 1 h. The mixture was concentrated, and the aqueous residue was washed with 1:1 hexane/ether. The aqueous phase was made basic with potassium hydroxide and extracted with methylene chloride. Drying over magnesium sulfate and concentration provided the title product as a yellow oil (1.33 g, 90%); NMR (CDCl3) 8.65 (m, 2H), 7.70-7.25 (6H), 2.20 (s, 3H).

b. Preparation of 4-(2-Acetylphenyl)pyridine. Using the same procedure, the title compound was prepared in 66% yield. NMR ($CDCl_3$) 8.65 (m, 2H), 7.66-7.25 (6H), 2.23 (s, 3H).

c. Preparation of 2-(2-Acetylphenyl)pyridine. Using the same procedure, the title compound was prepared in 29% yield. NMR ($CDCl_3$) 8.65 (m, 2H), 7.8-7.25 (6H), 2.20 (s, 3H).

d. Preparation of 4-(4-Acetylphenyl)pyridine. Using the same procedure, 4'-bromoacetophenone was converted to 1-(4-bromophenyl)-1,1-dimethylethane as a colorless liquid in 72% yield; NMR ($CDCl_3$) 7.55-7.30 (4H), 3.15 (s, 6H), 1.50 (s, 3H). This material was converted to the title compound in 97% yield: MP 94°C; NMR ($CDCl_3$) 8.75 (d, 2H), 8.10 (d, 2H), 7.70 (d, 2H), 7.50 (d, 2H), 2.65 (s, 3H).

The preparation of the compounds of Formula (I) by Methods A through C is described in greater detail in Examples 1 to 62. In these examples, all temperatures are in degrees Celsius. All reactions are performed under an atmosphere of dry nitrogen. Concentration under reduced pressure is performed with a rotary evaporator using a water aspirator. Chromatography refers to the method of medium-pressure column chromatography described by Still et al., J. Org. Chem. 1978, 43, 2923. The composition of solvent mixtures used as chromatographic eluents are given in percentages by volume. Nuclear magnetic resonance (NMR) spectra were obtained at a field strength of 200 or 300 MHz; abbreviations for NMR data are as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet, $CDCl_3$ = deuterochloroform solvent, DMSO-d6 = deutero-dimethylsulfoxide solvent, MeOH-d_4 = deuteromethanol solvent. Peak positions for NMR data are reported as parts per million downfield from the

internal standard tetramethylsilane. Mass spectra were obtained using methane chemical ionization; data are reported as the ratio of charge to mass of the parent ion.

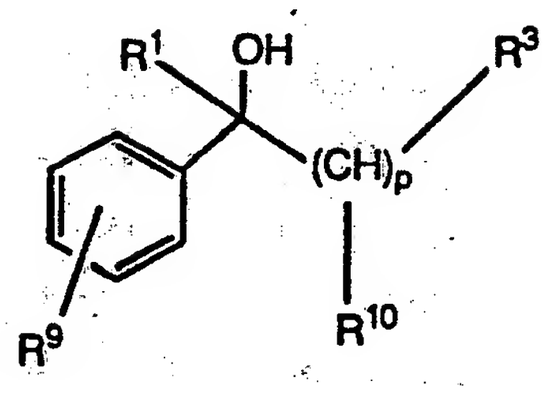
EXAMPLE 1

Preparation of 1-(4-Fluorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol

A mixture of 1-(4-fluorophenyl)-1-(4-bromophenyl)-2-(1-imidazolyl)ethanol (4.0 g, 0.011 mol), 4-pyridyltrimethylstannane (4.02 g, 0.016 mol), and bis(triphenylphosphine) palladium(II) chloride (0.7 g, 0.001 mol) was combined in 10:1 N,N-dimethylformamide/triethylamine (40 mL) and heated at 70° for 72 h. The mixture was cooled to room temperature, filtered through Celite® and the filter rinsed with methylene chloride. The filtrate was concentrated and the residue was dissolved in methylene chloride. The organic phase was washed with water and extracted with 1N hydrochloric acid. The acid extract was washed with ether and made basic with concentrated aqueous ammonia. The mixture was extracted with methylene chloride, the organic phase was washed with water, dried over magnesium sulfate and concentrated. The residue was chromatographed (9:1 methylene chloride/methanol) and the crude product was triturated in ether/hexane to provide the title product as a solid in 23% yield. MP 206-208°; NMR ($CDCl_3$) 8.65 (d, 2H), 7.72-6.92 (13H), 6.60 (d, 2H), 4.68 (s, 2H); Mass spec 360; Calcd. for $C_{22}H_{18}FN_{3O}$: C-72.84, H-4.96, N-11.58; Found: C-72.73, H-5.05, N-11.56.

Additional compounds of Formula (I) which were or may be prepared using the method of Example 1 are shown in Table 1.

TABLE 1



Ex.#	R^1	R^9	R^3	$(CHR^{10})_p$	mp (°C)
1	4-F-ph	4-(4-pyr)	1-imdz	CH_2	206-208
2	2,4-F_2-ph	4-(2-pyr)	1-imdz	CH_2	190-192
3	4-F-ph	4-(2-pyr)	1-imdz	CH_2	206-208
4	2,4-F_2-ph	4-(3-pyr)	1-imdz	CH_2	202-203
5	2,4-F_2-ph	4-(4-pyr)	1-imdz	CH_2	190-191
6	4-F-ph	3-(2-pyr)	1-imdz	CH_2	172-173
7	4-F-ph	3-(3-pyr)	1-imdz	CH_2	196-197
8	4-F-ph	3-(4-pyr)	1-imdz	CH_2	174-175
9	C_6H_5	4-(4-pyr)	1-imdz	CH_2	183-185
10	2-Cl-ph	4-(4-pyr)	1-imdz	CH_2	212-214
11	4-CH_3-ph	4-(4-pyr)	1-imdz	CH_2	184-186
12	4-CH_3O-ph	4-(4-pyr)	1-imdz	CH_2	202-203
13	4-F-ph	4-(4-pyr)	1-imdz	$(CH_2)_2$	
14	4-F-ph	4-(4-pyr)	1-imdz	$(CH_2)_4$	
15	4-F-ph	4-(4-pyr)	1-imdz	$CHCH_3$	
16	4-F-ph	4-(4-pyr)	1-imdz	$CH(C_4H_9)$	
17	2-thienyl	4-(3-pyr)	1-imdz	CH_2	
18	4-CH_3OCH_2-ph	3-(4-pyr)	1-(1,2,4-tz)	CH_2	
19	4-Cl-ph	4-(2-pyr)	1-imdz	$CHCH_3$	
20	2-thiazolyl	3-(3-pyr)	1-imdz	CH_2	

Footnotes for Table 1

ph = phenyl; pyr = pyridyl; imdz = imidazolyl; tz = triazolyl

EXAMPLE 21

Preparation of 1-(4-Trifluoromethylphenyl)-1-[4-(4-pyridyl)phenyl]- 2-(1-imidazolyl)ethanol

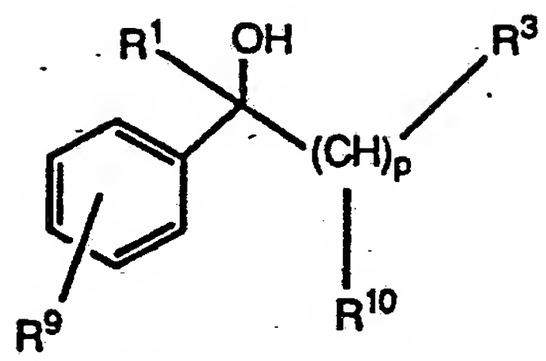
Part A. A solution of 4-(4-acetylphenyl)-pyridine (9.85 g, 0.05 mol) in acetic acid (500 mL) was treated with a 30% solution of hydrogen bromide in acetic acid (50 mL) and warmed to 75° to dissolve the resulting precipitate. The solution was cooled to 35°, and treated slowly with a solution of bromine in acetic acid (1.0 M; 50 mL, 0.05 mol). The mixture was then stirred for 30 min, warmed to 70° for 5 min, cooled to room temperature and stirred overnight. The mixture was concentrated and the residue was twice taken up in toluene and re-concentrated. The residue (17.4 g, 97%) was 2-bromo-4'-(4-pyridyl)-acetophenone hydrobromide. MP > 250°; NMR (MeOH-d_4) 8.90 (broad, 2H), 8.37 (d, 2H), 8.26 (d, 2H), 8.10 (d, 2H), 4.72 (S, 2H); Mass spec 358.

Part B. A slurry of the product of Part A (35.0 g, 0.098 mol) in tetrahydrofuran (300 mL) was treated with a solution of imidazole (40.0 g, 0.588 mol) in tetrahydrofuran (100 mL) and stirred at room temperature for 2 h. The mixture was concentrated and the residue was partitioned between water and methylene chloride. The aqueous layer was extracted with additional methylene chloride and the combined organic phases were were washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed (9:1 methylene chloride/methanol) and the crude product was twice taken up in toluene and concentrated, to provide 2-(1-imidazolyl)-4'-(4-pyridyl)-acetophenone (17.2 g, 66%) as yellow crystals. MP 144-146°; NMR (CDCl3) 8.92 (d, 2H), 8.10 (d, 2H), 7.80 (d, 2H), 7.55 (m, 3H), 7.15 (s, 1H), 6.97 (s, 1H); Mass spec 264.

Part C. A solution of 4-bromotrifluoromethylbenzene (8.54 g, 0.038 mol) in tetrahydrofuran (25 mL) was treated dropwise at -78° with n-butyllithium (1.6 M in hexane; 23.7 mL, 0.038 mol) and the mixture was stirred for 30 min. This was then transferred by a cannula to a second flask containing a slurry of cerium chloride (flame-dried under vacuum; 9.35 g, 0.038 mol) in tetrahydrofuran (25 mL) at -78°. The mixture was stirred at -78° for 60 min, then was treated with a solution of the product of Part B (2.0 g, 0.0076 mol) in tetrahydrofuran (30 mL) and the mixture was warmed to room temperature and stirred overnight. Saturated aqueous ammonium chloride (60 mL) was added, the mixture was diluted with water and extracted with methylene chloride. The organic phase was washed with water, dried over sodium sulfate and concentrated. The residue was chromatographed twice (3:1 ethanol/isopropanol, then 9:1 methylene chloride/methanol. Recrystallization (acetonitrile) provided the title compound as off-white crystals (0.50 g, 16%). MP 221-223°; NMR (CDCl3) 8.70 (d, 2H), 7.70 (10H), 7.32 (s, 1H), 6.90 (s, 1H), 6.70 (s, 1H), 6.55 (s, 1H), 4.95 (dd, 2H); Mass spec 410; Calcd. for $C_{23}H_{18}F_3N_3O$: C-67.48, H-4.43, N-10.26, F-13.92; Found: C-67.34, H-4.57, N-10.09, F-14.02.

Additional compounds which may be prepared using the method of Example 21 are shown in Table 2.

TABLE 2



Ex.#	R^1	R^9	R^3	R10	mp (°C)
21	4-CF_3-ph	4-(4-pyr)	1-imdz	H	221-223
22	4-Cl-ph	4-(4-pyr)	1-imdz	H	211-213
23	4-C_4H_9-ph	4-(4-pyr)	1-imdz	H	
24[1]	4-(CHO)-ph	4-(4-pyr)	1-imdz	H	209-211
25[2]	4-CH_3CO-ph	4-(4-pyr)	1-imdz	H	218-220
26	4-$(CH_2)_4N$-ph	4-(4-pyr)	1-imdz	H	
27	4-$(CH_3)_2N$-ph	4-(4-pyr)	1-imdz	H	105-107 d
28	2-thiazolyl	4-(4-pyr)	1-imdz	H	
29	3-thienyl	4-(4-pyr)	1-imdz	H	
30	2-pyr	4-(4-pyr)	1-imdz	H	
31	3-pyr	4-(3-pyr)	1-imdz	H	
32	3-Br-ph	3-(4-pyr)	1-imdz	H	
33	3,4-$(CH_3O)_2$-ph	4-(2-pyr)	1-imdz	H	
34	4-CH_3S-ph	4-(4-pyr)	1-imdz	CH_3	
35	4-CH_3SO_2-ph	4-(3-pyr)	1-imdz	H	
36	4-C_4H_9O-ph	3-(4-pyr)	1-imdz	H	
37	3-Cl-4-CH_3O-ph	4-(4-pyr)	1-imdz	H	
38	2,4-F_2-ph	4-(4-pyr)	1-(1,2,4-tz)	H	
39	2-furyl	4-(3-pyr)	1-imdz	H	
40	2-(N-CH_3)-pyrryl	3-(4-pyr)	1-imdz	H	

Footnotes for Table 2

ph = phenyl; pyr = pyridyl; imdz = imidazolyl; tz = triazolyl

[1] Prepared with the aldehyde protected as the dimethyl acetal; the acetal was hydrolyzed on work-up of the reaction.

[2] Prepared with the ketone protected as the dimethyl ketal; the ketal was hydrolyzed with dilute aqueous acid using standard methods.

EXAMPLE 41

Preparation of 1-(4-fluorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-benzimidazolyl)ethanol

Part A. A solution of 4-fluorophenylmagnesium bromide (prepared from 7.6 ml (0.070 mol) 4-bromofluorobenzene and 3.40 g (0.14 mol) magnesium turnings) in tetrahydrofuran (150 mL) was added to a suspension of 4-(4-acetylphenyl)pyridine (9.85 g, 0.050 mol) in tetrahydrofuran (50 mL) at 0°. The mixture was stirred for 30 min at 0° and for 30 min at room temperature, then was poured into saturated aqueous ammonium chloride. The mixture was extracted with ether, the organic phase was washed with water and brine, then was dried over magnesium sulfate and concentrated. The residue was recrystallized (1-chlorobutane) to give 1-(4-fluorophenyl)-1-[4-(4-pyridyl)phenyl]ethanol colorless needles (10.0 g, 68%). MP 166-170°; NMR ($CDCl_3$) 8.60 (d, 2H), 7.60-7.40 (8H), 7.00 (t, 2H), 2.00 (s, 3H).

Part B. A solution of the product of Part A (9.50 g, 0.032 mol) and p-toluenesulfonic acid hydrate (13.00 g, 0.068 mol) in chloroform (250 mL) was heated to boiling. Water and chloroform were removed by distillation, with additional chloroform added to

maintain the volume as needed. After 30 min, the mixture was cooled, concentrated to about 100 mL and diluted with ethyl acetate. The solution was washed with 1 M aqueous sodium bicarbonate, water and brine and was dried over magnesium sulfate and concentrated to provide 1-(4-fluorophenyl)-1-[4-(4-pyridyl)phenyl]ethylene (7.4 g, 84%) as a yellow oil. NMR ($CDCl_3$) 8.65 (m, 2H), 7.60 - 7.25 (8H), 7.00 (t, 2H), 5.50 (d, 2H).

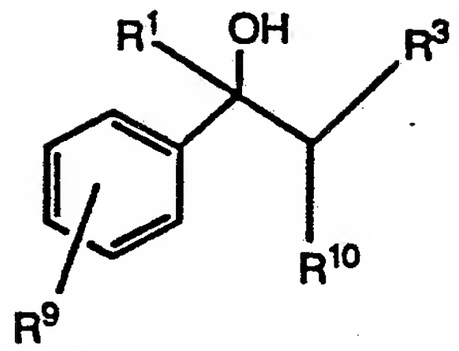
Part C. A solution of the product of Part B (6.30 g, 0.023 mol) in acetone (45 mL) was treated with N-methylmorpholine N-oxide hydrate (3.40 g, 0.025 mol) and water (15 mL). The resulting solution was treated with pyridine (7.5 mL) and a few crystals of osmium tetroxide and was heated at reflux for 24 h. Additional N-methylmorpholine N-oxide hydrate (0.34 g) was added and the solution was heated for an additional 16 h. The mixture was cooled to room temperature, diluted with ethyl acetate and washed with water. The water was back-extracted with ethyl acetate and the combined organic phases were washed with 95:5 water/glycerin, water and brine and dried over magnesium sulfate. The residue was 1-(4-fluorophenyl)-1-[4-(4-pyridyl)phenyl]-2-hydroxyethanol (6.8 g, 96%). NMR ($CDCl_3$) 8.50 (d, 2H), 7.60-7.10 (8H), 7.00 (t, 2H), 4.20 (dd, 2H), 2.35 (s, 2H).

Part D. A solution of the product of Part C (0.48 g, 1.52 mmol) in chloroform (8 mL) was treated with triethylamine (1.10 mL, 7.90 mmol). The solution was cooled to -25° and treated with methanesulfonyl chloride (0.15 mL, 1.98 mmol). The mixture was warmed to room temperature and stirred for 45 min. Water was added, the layers were separated and the organic phase was washed with water and brine and was dried over magnesium sulfate and concentrated. The residue was taken up in

benzene and concentrated, then was dissolved in N,N-dimethylformamide (7 mL). Benzimidazole (0.314 g, 2.66 mmol) and potassium tert-butoxide (0.298 g, 2.66 mmol) were added and the mixture was heated at 90° overnight. It was cooled to room temperature, diluted with water and extracted with ethyl acetate. The organic phase was washed with water and brine and was dried over magnesium sulfate and concentrated. The residue was chromatographed (95:5 methylene chloride/isopropanol) and the crude product was recrystallized (acetonitrile) to give the title compound (0.283 g, 45%) as a tan-yellow powder. NMR (DMSO-d_6) 8.60 (m, 2H), 8.85-7.40 (10H), 7.10-7.00 (4H), 6.55 (m, 1H), 5.15 (broad s, 2H); Calcd for $C_{26}H_{20}FN_3O \cdot H_2O$: C-74.76, H-5.06, N-10.04; Found: C-74.36, H-4.87, N-10.12.

Additional compounds which may be prepared using the method of Example 41 are shown in Table 3.

TABLE 3



Ex.#	R^1	R^9	R^3	R^{10}	mp (°C)
41	4-F-ph	4-(4-pyr)	1-bzim	H	206
42	4-F-ph	4-(4-pyr)	1-pyrrolyl	H	186-187
43	4-F-ph	4-(4-pyr)	1-indolyl	H	
44	4-F-ph	4-(4-pyr)	1-(1,2,4-tz)	H	119
45	3,4-F_2-ph	3-(4-pyr)	1-imdz	H	
46	4-F-ph	4-(4-pyr)	1-pyrazolyl	H	164-165
47	4-F-ph	4-(4-pyr)	1-bzim	CH_3	
48	2,4-Cl_2-ph	3-(4-pyr)	1-imdz	H	
49	3,4-Cl_2-ph	3-(2-pyr)	1-(1,2,4-tz)	H	
50	4-F-ph	4-(4-pyr)	1-(1,3,4-tz)	H	
51	3-Br-ph	4-(4-pyr)	1-(1,2,4-tz)	H	
52	2-Cl-ph	3-(4-pyr)	1-bzim	H	
53	3-CH_3O-ph	2-(4-pyr)	1-imdz	H	
54	4-F-ph	2-(4-pyr)	1-imdz	H	208
55	4-F-ph	2-(3-pyr)	1-imdz	H	138
56	2,4-F_2-ph	4-(3-pyr)	1-(1,2,4-tz)	CH_3	
57	2-thienyl	3-(3-pyr)	1-imdz	H	
58	2-(1-CH_3-imdz)	4-(4-pyr)	1-imdz	H	
59	2-F-ph	4-(4-pyr)	1-pyrrolyl	H	
60	2,4-$(CH_3O)_2$-ph	4-(4-pyr)	1-imdz	H	
61	4-$OHCH_2$-ph	4-(4-pyr)	1-imdz	H	173-175
62	4-CH_3OCO-ph	4-(4-pyr)	1-imdz	H	229-231

Footnotes for Table 3

bzim = benzimidazolyl

Examples of the preparation of compounds of formula (I) by functional group manipulation of other compounds of formula (I) are given in Examples 61 and 62.

EXAMPLE 61

Preparation of 1-(4-hydroxymethylphenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)-ethanol

A solution of the compound of Example 24 (0.20 g, 0.54 mmol) in methanol (25 mL) was treated with sodium borohydride (65 mg, 1.72 mmol) and stirred overnight at room temperature. The solution was concentrated, taken up in water and extracted with ethyl acetate. The extracts were washed with water, dried over magnesium sulfate and concentrated. The residue was chromatographed with 9:1 methylene chloride/methanol to give the title compound as off-white crystals (0.12 g, 60%). MP 173-175°C; NMR (DMSO-d_6) 8.62 (d, 2H), 7.70 (m, 4H), 7.60 (d, 2H), 7.45 (d, 2H), 7.32 (s, 1H), 7.25 (d, 2H), 6.87 (s, 1H), 6.65 (s, 1H), 6.25 (s, 1H), 5.15 (t, 1H), 4.87 (dd, 2H), 4.45 (d, 2H); Mass spec 371; Calcd. for $C_{23}H_{21}N_3O_2$: C-70.95, H-5.90, N-10.79; Found: C-71.13, H-5.89, N-10.30.

EXAMPLE 62

Preparation of 1-(4-methoxycarbonylphenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)-ethanol

Using the method of McDonald et al., J. Org. Chem. 1989, 54, 1213, the compound of Example 24 was converted to the title compound in 65% yield. MP 229-231°; NMR (DMSO-d_6) 8.9 (d, 2H), 8.62 (d, 2H), 7.75 (d, 2H), 7.7-7.6 (6H), 7.3 (s, 1H), 6.85 (s, 1H), 6.65 (s, 1H), 6.5 (s, 1H), 4.92 (dd, 2H), 3.82 (s, 3H); Mass spec 400; Calcd. for $C_{24}H_{21}N_3O_3 \cdot 3H_2O$: C-71.21, H-5.19, N-10.38; Found: C-71.20, H-5.22, N-10.33.

UTILITY

The compounds of Formula (I) have been shown to be efficacious in murine models of skin inflammatory diseases. One such model is inflammation induced by tetradecanoyl phorbol acetate (TPA), modified from the method of Kuehl et al., Nature, 1977, 265, 170; and Van Arman, Clin. Pharmacol. Ther., 1974, 16, 900. The TPA model mimics many of the inflammatory changes which occur in human diseases such as psoriasis, since elevated levels of inflammatory arachidonic acid metabolites are found and an influx of polymorphonuclear leukocytes is observed.

The test procedure used to evaluate the compounds of formula (I) is as follows: the test compound (100 mg/ear) was applied to the ears of mice in an appropriate vehicle, such as acetone, and then TPA, the inflammatory stimulus was applied to the right ear. Four hours later, the edema was measured by removing standard size discs from the ears using a biopsy punch. The weights of the ears were determined, and the suppression of the swelling observed in animals not treated with the test compound was determined.

Results obtained in this model for selected compounds of Formula (I) are shown in Table I.

TABLE I

Example	% inhibition of control swelling
1	72
2	51
3	63
4	52
5	73
6	61
7	64
8	69
9	46
10	63
11	62
12	74
21	66
22	79

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention are useful in the treatment of inflammatory diseases, including but not limited to rheumatoid arthritis, osteoarthritis, tendonitis, bursitis, psoriasis, contact dermatitis, eczema, inflammatory bowel disease, uveitis and conjunctivitis. Administration of the compounds of this invention can be by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be

administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will, of course, vary depending upon known factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; age, health and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment and the effect desired. Usually a daily dosage of active ingredient can be about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.5 to 50, and preferably 1 to 25 milligrams per kilogram per day given in divided doses 1 to 6 times a day or in sustained release form is effective to obtain desired results.

Compositions (dosage forms) suitable for internal administration contain from about 1 milligram to about 500 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms. It can also be administered by inhalation in the form of a nasal spray or lung inhaler. It can also be administered topically as an ointment, cream, gel, paste, lotion, solution, spray, aerosol, liposome, or patch. Dosage forms used to administer the active ingredient usually contain suitable carriers, diluents, preservatives or other excipients, as described in

Remington's Pharmaceutical Sciences, 17th Edition (1985) A. Osol, a standard reference text in the field.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, sucrose, mannitol, starch, cellulose derivatives, magnesium stearate, stearic acid and the like. Similar diluents can be used to make compressed tablets and powders. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose) and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration contain the active ingredient, suitable stabilizing agents and if necessary, buffer substances. Anti-oxidizing agents such as sodium bisulfite, sodium sulfite or ascorbic acid either alone or combined are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben and chloro-butanol.

The topical ointments, creams, gels and pastes can contain diluents such as waxes, paraffins, starch, polyethylene glycol, silicones, bentonites, silicic acid, animal and vegetable fats, talc and zinc oxide or mixtures of these or other diluents. Topical solutions

and emulsions can, for example, contain the customary diluents (with the exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples are water, ethanol, isopropanol, ethyl carbonate, benzyl alcohol, propylene glycol, oils, glycerol and fatty acid esters of sorbitol or mixtures thereof. Compositions for topical dosing may also contain preservatives or anti-oxidizing agents.

Powders and sprays can contain the usual diluents, such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicate and polyamide powders or mixtures of these materials. Aerosol sprays can contain the usual propellants. Liposomes can be made from such materials as animal or vegetable fats which will form lipid bilayers in which the active ingredient can be incorporated.

Patches can be made of a matrix such as polyacrylamide and a semipermeable membrane made from a suitable polymer to control the rate at which the material is delivered to the skin.

Examples of useful pharmaceutical compositions for administration of the compounds of this invention can be illustrated as follows:

CAPSULES: A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 50 mg of powdered active ingredient, 175 mg of lactose, 24 mg of talc and 6 mg of magnesium stearate.

SOFT GELATIN CAPSULES: A mixture of active ingredient in soybean oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 50 mg of the

active ingredient. The capsules are washed in petroleum ether and dried.

TABLETS: A large number of tablets are prepared by conventional procedures so that the dosage unit is 50 mg of active ingredient, 6 mg of magnesium stearate, 70 mg of microcrystalline cellulose, 11 mg of cornstarch and 225 mg of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

SUSPENSION: An aqueous suspension is prepared for oral administration so that each 5 mL contain 25 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P. and 0.025 mg of vanillin.

INJECTABLE: A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is sterilized by commonly used techniques.

NASAL SPRAY: An aqueous solution is prepared such that each 1 mL contains 10 mg of active ingredient, 1.8 mg methylparaben, 0.2 mg propyl-paraben and 10 mg methylcellulose. The solution is dispensed into 1 mL vials.

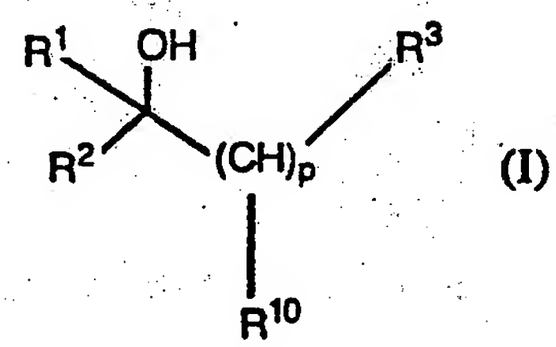
LUNG INHALER: A homogeneous mixture of the active ingredient in polysorbate 80 is prepared such that the final concentration of the active ingredient will be 10 mg per container and the final concentration of polysorbate 80 in the container will be 1% by weight. The mixture is dispensed into each can, the valves are crimped onto the can and the required amount of dichlorotetrafluoroethane is added under pressure.

OINTMENT: The active ingredient is added to a mixture of 48% by weight white petrolatum, 10% liquid petrolatum, 8% glycerol monostearate, 3% isopropyl myristate and 20% lanolin at 70°C. After thorough

mixing, a warm solution of methyl and propyl parabens in water containing sodium acetone bisulfite is added such that the final concentrations of each paraben is 0.15%, of water is 8%, and of sodium acetone bisulfite is 0.5%. The mixture is stirred until it has reached room temperature.

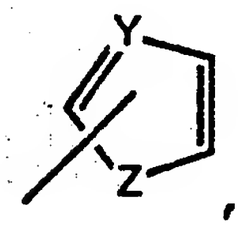
WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

in the form of an individual stereoisomer, a non-racemic stereoisomer mixture or a racemic mixture or a pharmaceutically acceptable salt thereof wherein:

R^1 is 2-, 3-, or 4-pyridyl,  , R^7, or phenyl optionally substituted with 1-3 substituents independently selected from the group consisting of F, Cl, Br, C_1-C_4 alkyl, C_1-C_4 perfluroalkyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, CHO, $COOR^4$, C_1-C_4 acyl, NR^5R^6, C_1-C_4 alkoxy or CH_2OR^8;

R^2 and R^7 independently are phenyl substituted in the ortho, meta, or para position with R^9;

R^3 is imidazole, 1,2,4-triazole, 1,3,4-triazole, benzimidazole, pyrrole, indole, or pyrazole provided that R^3 is bonded to the remainder of the structure through a nitrogen atom;

R^4, R^8, and R^{10} independently are H or C_1-C_4 alkyl;

R^5 and R^6 independently are H, C_1-C_4 alkyl, or taken together are $(CH_2)m$ wherein m is 4-5;

R^9 is 2-, 3-, or 4-pyridyl;

Y is N or CH;

Z is S, O, or NR^{11};

R^{11} is H or C_1-C_4 alkyl; and

p is 1-4 provided that when p is greater than 1, then R^{10} is H.

2. A compound of claim 1 wherein p is 1.

3. A compound of claim 1 wherein R^3 is imidazole or triazole.

4. A compound of claim 1 wherein p is 1 and R^3 is imidazole or triazole.

5. A compound of claim 3 wherein R^3 is imidazole.

6. A compound of claim 4 wherein R^3 is imidazole.

7. A compound of claim 1 wherein R^{10} is H.

8. A compound of claim 4 wherein R^{10} is H.

9. A compound of claim 1 wherein R^1 is phenyl optionally substituted by one or two substituents independently selected from the group consisting of F, Cl, Br, C_1-C_4 alkyl, C_1-C_4 perfluoroalkyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, CHO, $COOR^4$, C_1-C_4 acyl, NR^5R^6, C_1-C_4 alkoxy or CH_2OR^8.

10. A compound of claim 4 wherein R^1 is phenyl optionally substituted by one or two substituents independently selected from the group consisting of F,

Cl, Br, C_1-C_4 alkyl, C_1-C_4 perfluoroalkyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, CHO, $COOR^4$, C_1-C_4 acyl, NR^5R^6, C_1-C_4 alkoxy or CH_2OR^8.

11. A compound of claim 1 wherein:
R^3 is imidazole;
R^{10} is H; and
R^1 is phenyl optionally substituted by one or two substituents independently selected form the group consisting of F, Cl, Br, C_1-C_4 alkyl, C_1-C_4 perfluoroalkyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, CHO, $COOR^4$, C_1-C_4 acyl, NR^5R^6, C_1-C_4 alkoxy or CH_2OR^8.

12. A compound of claim 4 wherein:
R^3 is imidazole;
R^{10} is H; and
R^1 is phenyl optionally substituted by one or two substituents independently selected form the group consisting of F, Cl, Br, C_1-C_4 alkyl, C_1-C_4 perfluoroalkyl, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, CHO, $COOR^4$, C_1-C_4 acyl, NR^5R^6, C_1-C_4 alkoxy or CH_2OR^8.

13. A compound of claim 11 wherein R^1 is mono- or di-substituted phenyl with one of the substituents at the 4-position.

14. A compound of claim 11 wherein R^2 is 4-(4-pyridylphenyl) or 3-(4-pyridylphenyl).

15. A compound of claim 11 wherein:

R^1 is mono- or di-substituted phenyl with one of the substituents at the 4-position; and

R^2 is 4-(4-pyridylphenyl) or 3-(4-pyridylphenyl).

16. The compound of claim 15 which is 1-(4-fluorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

17. The compound of claim 15 which is 1-(2,4-difluorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

18. The compound of claim 15 which is 1-(4-fluorophenyl)-1-[3-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

19. The compound of claim 15 which is 1-(4-methylphenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

20. The compound of claim 15 which is 1-(4-methoxyphenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

21. The compound of claim 15 which is 1-(4-trifluoromethylphenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

22. The compound of claim 15 which is 1-(4-chlorophenyl)-1-[4-(4-pyridyl)phenyl]-2-(1-imidazolyl)ethanol.

23. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 1.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 2.

25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 3.

26. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 4.

27. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 5.

28. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 6.

29. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 7.

30. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 8.

31. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 9.

32. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 10.

33. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 11.

34. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 12.

35. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 13.

36. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 14.

37. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of a compound of claim 15.

38. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of the compound of claim 16.

39. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of the compound of claim 17.

40. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of the compound of claim 18.

41. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of the compound of claim 19.

42. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of the compound of claim 20.

43. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of the compound of claim 21.

44. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-inflammatory effective amount of the compound of claim 22.

45. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 1.

46. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 2.

47. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 3.

48. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 4.

49. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 5.

50. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 6.

51. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 7.

52. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 8.

53. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 9.

54. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 10.

55. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 11.

56. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 12.

57. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 13.

58. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 14.

59. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of a compound of claim 15.

60. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of the compound of claim 16.

61. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of the compound of claim 17.

62. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of the compound of claim 18.

63. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of the compound of claim 19.

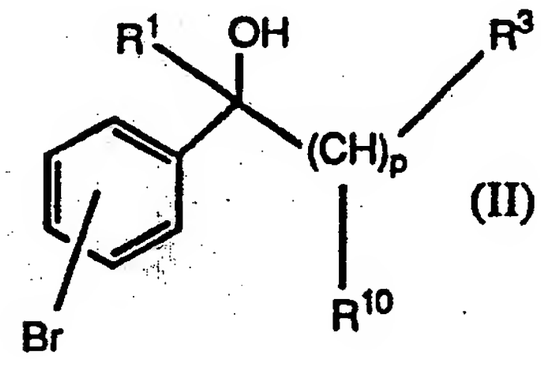
64. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of the compound of claim 20.

65. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of the compound of claim 21.

66. A method of treating an inflammatory disease in a mammal comprising administering to the mammal an anti-inflammatory effective amount of the compound of claim 22.

67. A process for preparing the compounds of claim 1 comprising:

a) reacting in the presence of an appropriate transition metal catalyst, a compound of the formula:



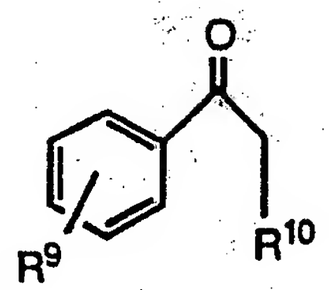
(II)

where R^1, R^3 and R^{10} are as defined in claim 1;

b) with a compound of the formula:
R^9SnR
where R^9 is as defined in claim 1 and R is alkyl of 1-4 carbons.

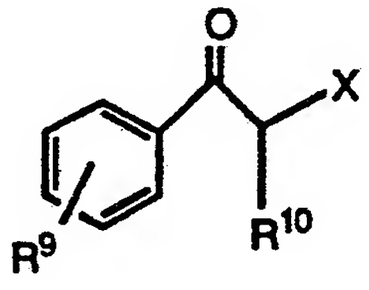
68. A process for preparing the compounds of claim 1 wherein p is 1 comprising:

a) reacting a pyridylphenyl ketone of the formula:



(III)

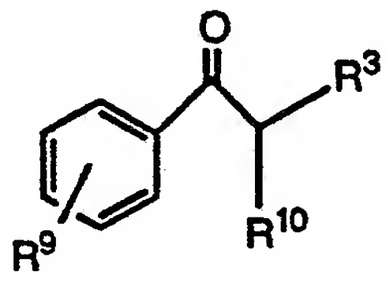
with an appropriate reagent in the presence of an acidic catalyst to yield an alpha-halo derivative of the formula:



(IV)

where X is bromine or chlorine;

b) reacting the halo-derivative with a nitrogen heterocycle (R^3H) or optionally with a metal salt of a heterocycle R^3M (where M is Na or K) to yield a compound of formula:

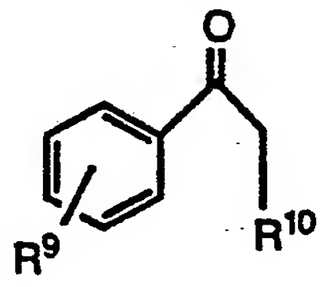


(V); and

c) reacting the compound of step b with an organometallic compound R^1M^1 (where M^1 is lithium, magnesium halide or cerium halide).

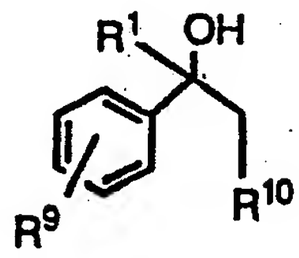
69. A process for preparing a compound of claim 1 where p is 1 comprising:

a) reacting a pyridylphenyl ketone of the formula:



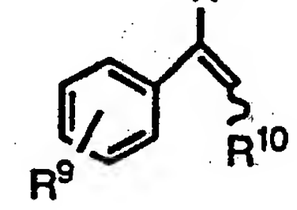
(III)

with an appropriate aryl organometallic reagent to yield a compound of formula:



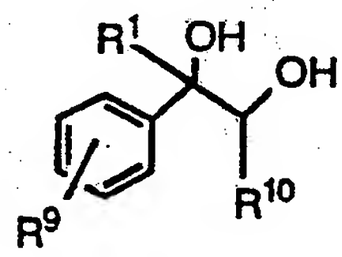
(VI);

b) dehydrating the alcohol (VI) to yield the olefin of formula:



(VII);

c) oxidizing the olefin (VII) optionally in the presence of an auxiliary oxidant to yield a compound of formula:



(VIII); and

d) reacting a compound of formula (VIII) with a sulfonyl chloride such as methanesulfonyl chloride or p-toluenesulfonyl chloride in the presence of pyridine or triethylamine, followed by reacting the intermediate with a nitrogen heterocycle R^3H or optionally a metal salt of a nitrogen heterocycle R^3M (where M is Na or K).

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/00022

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 401/10,409/14,417/14,401/14,405/14,
A 61 K 31/445,31/425

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 401/00,C 07 D 409/00,C 07 D 417/00, C 07 D 405/00,A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4 859 693 (BATT) 22 August 1989 (22.08.89), see claims 1,6 (cited in the application). --	1, 23-44
A	DE, A1, 3 345 813 (BOEHRINGER) 27 June 1985 (27.06.85), see claims 1,10. --	1,23
A	DE, A1, 3 413 173 (BAYER) 17 October 1985 (10.10.85), see claim 1. --	1
A	DE, A1, 2 920 375 (BAYER) 20 November 1980 (20.11.80), see claim 1 (cited in the application). --	1
A	DE, A1, 3 813 841 (BAYER) 15 December 1988 (15.12.88), see claim 1, page 19, lines 9-13.	1

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 April 1991	21. 05. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. PEIS M. Peis

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	DE, A1, 2 732 750 (MERCH) 08 February 1979 (08.02.79), see claims 1,5.	1,23
A	Chemical Abstracts, Volume 108, no. 15, issued 1988, April 11 (Columbus, Ohio, USA), Boyadzhiev, S. et al. "Preparation and absolute configuration of some 1-aryl-1-(2-pyridyl)propanes", see page 728, column 2, the abstract no. 131 539d, Izv. Khim. 1987, 20(2), 206-14 (Eng).	1
A	Chemical Abstracts, Volume 111, no. 15, issued 1989, October 9 (Columbus, Ohio, USA), Boyadzhiev, S. et al. "Conformational analysis of some substituted aryl-2-pyridylmethanes", see page 687, column 2, abstract no. 133 388q, Izv. Khim. 1988, 21(2), 201-7 (Eng).	1

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 45-66 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1 (iv)
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANHANG
zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX
to the International Search Report to the International Patent Application No.

ANNEXE
au rapport de recherche international relatif á la demande de brevet international n°

PCT/US91/00022 SAE 44179

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The Office is in no way liable for these particulars which are given merely for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les reseignements fournis sont donnés á titre indicatif et n'engagent pas la responsibilité de l'Office.

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
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